Title
History of Psychopharmacology.

Journal
Annual review of clinical psychology, 15(1)

ISSN
1548-5943

Authors
Braslow, Joel T
Marder, Stephen R

Publication Date
2019-05-01

DOI
10.1146/annurev-clinpsy-050718-095514

Peer reviewed

ANNUAL REVIEWS

Annual Review of Clinical Psychology

History of Psychopharmacology

Joel T. Braslow[1,2] and Stephen R. Marder[1,3]

[1]Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine, University of California, Los Angeles, California 90095-1759, USA; email: jbraslow@mednet.ucla.edu

[2]Department of History, University of California, Los Angeles, California 90095-1759, USA

[3]Veterans Administration Desert Pacific Mental Illness Research, Education, and Clinical Center, Los Angeles, California 90073, USA

Annu. Rev. Clin. Psychol. 2019. 15:25–50

First published as a Review in Advance on February 20, 2019

The *Annual Review of Clinical Psychology* is online at clinpsy.annualreviews.org

https://doi.org/10.1146/annurev-clinpsy-050718-095514

Keywords

psychopharmacology, history, antipsychotics, antidepressants, mental illness, treatment

Abstract

We live in an age of psychopharmacology. One in six persons currently takes a psychotropic drug. These drugs have profoundly shaped our scientific and cultural understanding of psychiatric disease. By way of a historical review, we try to make sense of psychiatry's dependency on psychiatric drugs in the care of patients. Modern psychopharmacology began in 1950 with the synthesis of chlorpromazine. Over the course of the next 50 years, the psychiatric understanding and treatment of mental illness radically changed. Psychotropic drugs played a major part in these changes as state hospitals closed and psychotherapy gave way to drug prescriptions. Our review suggests that the success of psychopharmacology was not the consequence of increasingly more effective drugs for discrete psychiatric diseases. Instead, a complex mix of political economic realities, pharmaceutical marketing, basic science advances, and changes in the mental health-care system have led to our current infatuation with psychopharmacology.

Contents

1. INTRODUCTION 26
2. PSYCHOPHARMACOLOGY BEFORE THERE WAS PSYCHOPHARMACOLOGY: MID-NINETEENTH CENTURY TO 1950 ... 27
3. CREATION OF MODERN PSYCHOPHARMACOLOGY: 1950–1964 28
   3.1. Discovery and Serendipity 28
   3.2. Market Expansion 29
   3.3. Clinical Accounts 29
   3.4. Tricyclic Antidepressants, Monoamine Oxidase Inhibitors, Minor Tranquilizers, and Lithium 31
   3.5. Psychopharmacology in Context 33
   3.6. Psychopharmacology in Everyday Clinical Practice 34
4. FORGING DISEASE SPECIFICITY: 1964–1988 35
   4.1. Creating Neuroscience 37
   4.2. The Randomized Controlled Trial 39
   4.3. Narrowing Clinical Responsibility 40
5. HOPE AND ITS DISCONTENTS: LATE 1980s TO THE PRESENT 41
   5.1. Rediscovery of Clozapine and Atypical Antipsychotic Drugs 42
   5.2. Better than Well: The Rise of the SSRIs 43
   5.3. Pharmaceutical Profits and Psychotropic Drugs 43
   5.4. A Darker Side 44
6. CONCLUSIONS 46

1. INTRODUCTION

> It was definitely a clinical depression and one that I was going to have to have help to overcome. What I learned about it is your brain needs a certain amount of serotonin and when you run out of that, it's like running out of gas, it's like you're on empty. (Tipper Gore 1999, quoted in Hall 1999, p. A1)

The past 50 years could easily be characterized as the age of psychopharmacology. From a cultural perspective, Prozac (fluoxetine; Eli Lilly and Company) has replaced Freud as shorthand for talking about what ails us. From an economic perspective, we spend more money on psychotropic drugs than on any other class of pharmaceuticals. From a clinical perspective, especially in the case of psychiatry, psychiatrists have become much more comfortable writing a prescription for an antidepressant than interpreting a patient's unconscious motivations. From a scientific perspective, psychotropic drugs have made possible fundamental insights into how the brain functions.

Knowing her words would appear in America's most widely read national daily newspaper, *USA Today*, Tipper Gore no doubt intentionally simplified her explanation for her depression and how she fixed it. An advocate for better mental health care, Gore hoped her public confession would encourage others to seek treatment. Unpacking her quotation, she believes that her sadness was a disease like any other biological disease, rooted in biology with a specific pathophysiology. Importantly, it is a pathophysiology that is explained by a deficiency of serotonin. As a "clinical depression," her biological explanation suffices as a complete-enough description. Any other details about her life and relationships are extraneous to her real problem, her serotonin-depleted brain, which presupposes cure by a selective serotonin reuptake inhibitor (SSRI). Her explanation for her depression expresses a commonsense truth that we now take for granted and that we use

simultaneously to explain as well as fix our distressed psyches. Our aim is to describe how this now almost-too-obvious fact became fact. The story is more complicated than we might think.

Humans have used psychoactive substances since long before the advent of psychiatry, but the modern history of psychopharmacology begins in 1950. We chronicle four different eras. The first, the prehistory of modern psychopharmacology, spans from the mid-nineteenth century to 1950. The second, the golden age of psychopharmacology, begins with the synthesis of chlorpromazine in 1950 and ends in the mid-1960s. Researchers discovered all of our current psychotropic drug classes in this moment of unrivaled productivity. Paradoxically, psychiatrists embraced these new drugs with ambivalence, generally using them as adjuncts to what they saw as their more important psychosocial and psychotherapeutic activities. Spanning from the mid-1960s to the late 1980s, the third era marked startling and unprecedented changes for psychiatry, the science of the brain, the fate of patients, and the commonsense vision of disease and therapeutics that we now take for granted. Psychotropic drugs played a central part in these dizzying changes. Our fourth era, the heyday of blockbuster antidepressants and antipsychotics, begins with the introduction of Prozac in 1988 into the US market. Over 30 years, the new drugs promised to radically transform the landscape of mental illness, but as the original patents expire, recent clinical trials have created doubt about their unalloyed benefits.

2. PSYCHOPHARMACOLOGY BEFORE THERE WAS PSYCHOPHARMACOLOGY: MID-NINETEENTH CENTURY TO 1950

Nineteenth-century asylum physicians were notorious for their liberal use of sedatives and hypnotics, including such drugs as bromides, chloral hydrate, hyoscine, paraldehyde, sulfonal, and narcotics (Ackerknecht 1979). Physicians rarely claimed that these drugs actually treated mental illness, rather they sedated, calmed, and soothed. Yet like physical restraint, according to most practitioners, they hardly counted as treatment.

Occasionally, especially at its first introduction, one finds an enthusiastic report on the effects of a particular sedative drug. For example, describing the effects of hyoscine, Drapes (1889, p. 942) wrote: "It is incomparably superior to the older sedatives, such as morphine and chloral, and none of the newer ones, in my opinion, approach it in value as a remedy for controlling paroxysms of furious excitement and turbulent maniacal outbreaks." Enthusiasm for hyoscine was short-lived. The famous late-nineteenth-century British psychiatrist, Henry Maudsley (1895, p. 557) wrote that "the reports of its successes, when examined, are mostly naive reports of its success, not in curing but in 'quieting the patient.'" For Maudsley, pharmaceutical agents, although useful, were not curative: "Drugs can no more directly quell an insane delusion than they can eradicate an envy or abate an ambition" (Maudsley 1895, p. 546). Raising concerns similar to those that would be expressed about the new tranquilizing agents more than 50 years later, Maudsley cautioned:

> Mechanical restraint, except under surgical necessities, was formerly abandoned…because it was deemed better for the patient to let him have the relief and self-respect of pretty free exercise than to keep him tied up like a mad dog…but it may be doubted whether its coarse bond did as much harm as has been done by the finer means of chemical restraint which have been used to paralyse the brain and render the patient quiet. (Maudsley 1895, pp. 554–55)

The barbiturates were among the first new psychotropic drug discoveries of the twentieth century. Discovered by Emil Fischer and Joseph von Mering in 1903, barbiturate acid and its derivatives proved simple and easy to administer and joined the nineteenth-century sedatives and hypnotics as useful, although not terribly therapeutic, interventions.

3. CREATION OF MODERN PSYCHOPHARMACOLOGY: 1950–1964

The synthesis of chlorpromazine [marketed in the United States as Thorazine; Smith, Kline & French (SKF)] in 1950 marks the beginning of modern psychopharmacology. Unlike the sedatives and hypnotics, chlorpromazine was the first psychoactive agent that psychiatrists believed actually treated their patients' mental ills instead of merely masking the underlying disease. Chlorpromazine also inaugurated the most remarkable decade in the history of psychopharmacology. During that decade, the pharmaceutical industry synthesized and marketed compounds that came to define the future classes of psychotropic drugs. The list includes the antipsychotic drugs (chlorpromazine), anxiolytic drugs (meprobamate in 1950, chlordiazepoxide in 1955), monoamine oxidase inhibitor (MAOI) antidepressants (iproniazid in 1951), and the tricyclic antidepressants (imipramine in 1951).

3.1. Discovery and Serendipity

Largely by luck, clinicians stumbled upon the psychotropic effects of these agents. Chlorpromazine itself was the most famous case. Synthesized by Paul Charpentier of the French pharmaceutical company Rhône-Poulenc, chlorpromazine was the culmination of a long process that began in the mid-1800s with the production of synthetic dyes from coal tars. Organic chemist August Bernthsen in 1883 identified and named the core structure, which he called a phenothiazine nucleus, a structure seen both in dyes such as methylene blue and in chlorpromazine (Kerner & McCoy 2017).

In the 1930s and 1940s, researchers became increasingly interested in producing synthetic antihistamines. This led Charpentier to modify and test for antihistaminic properties several phenothiazine compounds. Promethazine was one of his early successes in 1947. Unlike contemporary strict controls on testing new drugs, informal contacts with physicians were used by companies to test newly synthesized compounds. In 1949, French military surgeon Henri Laborit tested a small amount of promethazine as a preventative for shock and noted that it produced a "euphoric quietude" in patients (Swazey 1974).

Charpentier continued working on further iterations of the phenothiazine nucleus, hoping to generate even greater antihistaminic effects. On December 11, 1950, he synthesized R.P. 4560. Rhône-Poulenc sent this new compound to several Paris physicians, including Laborit at the Val-de-Grâce and psychiatrists Pierre Deniker and Jean Delay at the Centre Hospitalier Sainte-Anne. Laborit was struck by the new compound's ability to calm anxious patients without too much sedation, and he encouraged a number of psychiatrist colleagues to try the new drug on their patients. Deniker and Delay, meanwhile, reported in May 1952 on the ability of the drug to calm psychotically agitated patients. That same year, the American pharmaceutical company SKF bought the North American rights to chlorpromazine and received US Food and Drug Administration (FDA) approval to market it as Thorazine in May 1954.

Given the growing number of positive reports from France, SKF was fairly confident in the drug's psychiatric applications. In the advertisement introducing chlorpromazine to American psychiatrists in the May 1954 issue of the *American Journal of Psychiatry*, SKF announced: "'Thorazine' is useful in controlling anxiety, tension, agitation, confusion, delirium, or hostility, whether occurring in schizophrenic, manic-depressive, toxic, or functional states" (Farrar 1954). SKF also marketed Thorazine for a variety of other ills, ranging from vomiting (its original FDA indication), nausea, and pruritus to hiccups. Rhône-Poulenc also recognized the many potential uses of the new drug that it branded Largactil. (Swazey 1974, Grob 1994, Shorter 1997). SKF soon realized that the psychiatric market was by far the most important. By 1956, four million patients in the United States had taken chlorpromazine—primarily for psychiatric reasons—yielding

$75 million in profits in 1955 alone (Overholser 1956, p. 198) and far exceeding SKF's wildest expectations of returns on its $350,000 investment (Scull 2015). Over the next decade, Thorazine sales drove the company's rapid growth, from net sales of $53 million in 1953 to $347 million in 1970 (Scull 2015).

3.2. Market Expansion

Another drug with similar clinical properties to but very different origins from chlorpromazine was introduced to North American psychiatry in 1954. It was derived from the plant *Rauwolfia serpentina*, which been used in India for centuries for diverse ills including snake bites, fevers, madness, and in the twentieth century, hypertension. Ciba isolated the active salt from the plant in 1953 and named it reserpine; company pharmacologist Fredrick Yonkman tested the new compound on animals and used the word tranquilizer to describe the effects. Leading American psychiatrist Nathan S. Kline, interested in the psychiatric potential, convinced Ciba to undertake a study at Rockland State Hospital in New York. In 1953, Kline tested the drug first on himself and research staff, then on patients, and presented his results to the New York Academy of Sciences the following year (Kline 1954). Reserpine was used extensively in the mid-to-late 1950s, but its popularity waned due to its longer onset of action compared with chlorpromazine, propensity to cause hypotension, and a growing number of reports that some patients become profoundly depressed after taking it (Healy & Savage 1998).

The core reserpine molecule was not easily manipulated, but the phenothiazine core molecule was, allowing pharmaceutical companies to create similarly acting compounds. By 1964, pharmaceutical companies had synthesized, tested, and brought to market more than a dozen new phenothiazines—for example, Sparine (promazine; American Home Products), Vesprin (triflupromazine; Bristol-Myers Squibb), Tentone (methoxypromazine; Lederle), Stelazine (trifluoperazine; SKF), Prolixin (fluphenazine; Bristol-Myers Squibb), Mellaril (thioridazine; Sandoz), and Pacatal (pecazine; Warner Chilcott)—but none achieved the fame and profits that Thorazine had generated for SKF.

3.3. Clinical Accounts

Psychiatrists did not routinely use the term antipsychotic until the late 1960s and 1970s. Instead, reflecting the drugs' clinical uses, psychiatrists used the terms major tranquilizers, ataractics, and neuroleptics. The term major tranquilizer was employed quite early on to distinguish these drugs from the minor tranquilizers such as meprobamate (see Section 3.4.3). A 1962 account made the following comparison.

> The Major Tranquilizers are characterized by the following points:
>
> 1. These drugs produce…emotional calmness with relatively little sedation; they have proved useful in controlling the symptoms of acutely and chronically disturbed psychotic patients.
> 2. They are capable of producing the reversible extrapyramidal syndrome characterized by rigidity, tremors, and drooling.
> 3. Annoying side reactions [are] relatively high with these drugs, and serious dangers do exist to some extent.
> 4. They produce little, if any, dependency.
>
> The Minor Tranquilizers are characterized by other points:
>
> 1. These drugs produce calmness or relaxation, but not of the same quality as that produced by the major tranquilizers….They are useful in the treatment of psychoneurotic problems and common nervous tension.

2. They do not produce extrapyramidal motor phenomena so characteristic of the major tranquilizers.
3. Annoying side reactions with the use of these drugs is relatively low. Dangerous reactions are rare.
4. Habituation may occur. (Benson & Schiele 1962, pp. 5–7)

Delay and Deniker introduced the term neuroleptic in 1955 to emphasize the "extrapyramidal motor phenomena" caused by the major tranquilizers. Derived from the Greek, *leptic* means to take hold or to seize, while *neuro* refers to the brain. Delay and Deniker believed that a crucial action of chlorpromazine was to produce a state of "psychomotor indifference" that was especially effective in quelling psychotic agitation and that the therapeutic calm was produced by the same mechanism that led to the extrapyramidal motor side effects (Healy 2002, p. 117). European psychiatrists used the term neuroleptic more widely than Americans (López-Muñoz et al. 2005). Psychiatrists also used the term ataractic, suggested by Laborit and derived from the Greek *ataraxy*—not disturbed, calm—to describe chlorpromazine. Antipsychotic, the currently accepted term, first coined by Heinz E. Lehmann in 1956 in an address to the Canadian Medical Association, did not achieve widespread acceptance until the 1960s (Lehmann 1993, p. 300).

The range of terms reflects the varied biological effects of these new drugs. Willis Bower (1954) at McLean Hospital conducted a trial of chlorpromazine in 1953 and published his findings in the *New England Journal of Medicine* in 1954. In his open trial, he treated a total of 29 patients diagnosed with the following disorders: manic psychoses, acute schizoaffective psychoses with manic features, acute confusional schizophrenia, excited chronic schizophrenia, depressions, anxiety states, and senile and arteriosclerotic psychoses. He found both good and poor results across all disease categories. As in many early reports on phenothiazines, he expressed cautious, muted optimism: "Chlorpromazine may have some effect on the agitation or excitement of chronic schizophrenia; it appears to induce calm without changing mental content significantly….The drug does not appear to diminish hallucinosis" (Bower 1954, p. 692). In the first *JAMA* study on chlorpromazine, William Winkelman (1954) reported on 142 patients; he found it effective but not a replacement for other therapies, especially psychotherapies.

Similarly, early reports in the *American Journal of Psychiatry* emphasized the broad range of indications for chlorpromazine.

> It may be applied to the treatment of all conditions in which vegetative disturbances play a role, such as anxiety states, severe neurosis—including obsessions—symptoms following drug withdrawal, manic-depressive disorders, certain cases of acute and florid schizophrenia, and in a wide variety of psychosomatic disorders. (Wortis 1954, p. 508)

Another author wrote that chlorpromazine had a place in "most types of mental disorder" (Kinross-Wright 1954, p. 298).

Chlorpromazine was especially useful in quelling extreme forms of violence and agitation.

> The patients were selected because they were difficult nursing problems….The symptomatology displayed by these patients was manifested by one or several of the following factors—extremely noisy for prolonged periods of time, confusion of such a degree that they needed constant supervision, agitated, destructive, hyperactive, impulsively assaultive, denudative, smearing, soiling, requiring repeated seclusion and sedation. (Kurland 1955, p. 322)

"Agitated, destructive, hyperactive, impulsively assaultive, denudative, smearing, soiling" behaviors had led psychiatrists to give electroconvulsive therapy (ECT) and, if unsuccessful, lobotomy;

they quickly learned that phenothiazines were easier to prescribe and produced more reliable outcomes, substantially diminishing the need for these drastic somatic treatments (Braslow 1997). Lobotomy had spread throughout Western Europe and North America in the late 1940s as a treatment of last resort for violent, extremely disturbed, and uncontrollable patients with psychoses. Although chlorpromazine not infrequently produced a kind of apathy or indifference, similar to that produced by lobotomy, it was the drug's ability to replace the irreversible surgery that led to its occasional description as a "chemical lobotomy" (Anton-Stephens 1954, Lehmann 1955).

The following case example, from a California state hospital patient record, illustrates why chlorpromazine was so useful in the practical, everyday context of clinical care for individuals for whom all previous interventions had failed. Admitted in 1942 and diagnosed with dementia praecox, E. M. was in her late twenties, married and, on admission, was "delusional and confused." She continued to be psychotic and when she became increasingly aggressive, was given hundreds of ECT treatments. When she remained unimproved, her doctors lobotomized her in 1948, but with limited success. In a 1955 progress note, her physician wrote:

> She remains unpredictable and aggressive and is quite uncooperative on the ward. A more radical type of operation might be of benefit to the patient….Another method of possibly giving the patient high doses of Thorazine might be equally successful. Prefrontal lobotomy denied.

Fortunately, E. M. improved sufficiently on chlorpromazine, avoiding the more radical lobotomy. In fact, in California state hospitals, not a single lobotomy was performed after the introduction of chlorpromazine (Braslow 1997).

3.4. Tricyclic Antidepressants, Monoamine Oxidase Inhibitors, Minor Tranquilizers, and Lithium

The antidepressants, MAOIs, minor tranquilizers, and lithium are each important in their own right. Not only have they each played an important part in how we conceptualize and care for individuals with mental illness, they also have had enormous significance for the pharmaceutical industry and our broader cultural conceptions of mental distress. They, too, came into existence during the same postwar period that gave birth to chlorpromazine; and their psychoactive properties were likewise discovered by good luck.

3.4.1. Tricyclic antidepressants. The tricyclic antidepressants are an excellent case in point. Like numerous other pharmaceutical companies in 1955, Geigy scrambled to synthesize a drug to compete with the spectacular success of chlorpromazine and gave one promising compound, an iminodibenzyl, to Swiss psychiatrist Roland Kuhn to test. Kuhn tested the drug at the Münsterlingen Cantonal Asylum and wrote to Geigy in August 1956 to emphasize that while it had none of the tranquilizing and antipsychotic effects observed with chlorpromazine, the new compound "has an obvious effect on depression. The vital depression visibly improves" (Shorter 2008, p. 60). Nevertheless, Kuhn published his findings on imipramine (trade name Tofranil) in August 1957 (Healy 1997, p. 52).

Geigy launched the drug in 1957 in Switzerland. Kuhn's first American publication on imipramine appeared in 1958, summarizing his treatment of more than 500 patients with a variety of diagnoses (Kuhn 1958). He concluded:

> It was demonstrated that the compound has potent antidepressant action. Best responses were obtained in cases of endogenous depression showing typical symptoms of mental and motor retardation, fatigue, feeling of heaviness, hopelessness, guilt, and despair. (Kuhn 1958, p. 464)

Two points deserve emphasis. First, Kuhn's careful clinical observations of imipramine's antidepressant properties would have failed to meet any of our contemporary standards for clinical trials. He had no control group; he utilized no rating scales; and he was not blinded to the treatment. Yet he made a fundamental discovery although or, more likely, because he was unhindered by any preconceptions that a more formal clinical trial might have imposed. As discussed in Section 4.2, the introduction of the randomized controlled trial (RCT) into the evaluation of psychotropic drugs was not simply the introduction of a neutral method. Instead, the RCT shaped the very ways in which illness was (and is) conceptualized.

Second, imipramine (and, almost simultaneously, the MAOIs) helped to define a new disease entity, namely depression. ECT and amphetamines helped to establish depressive states and neurotic depression as treatable disorders (Rasmussen 2006). But the use of imipramine and, even more so, amitriptyline emphasized the importance and prevalence of depression. The manufacturer of amitriptyline (trade name Elavil), Merck, asked a number of psychiatrists to evaluate its possible antipsychotic properties in 1958. Frank Ayd thought that amitriptyline, given its molecular similarity to imipramine, probably had antidepressant properties. In 1960, he reported on the outcome of 130 "office and hospitalized patients…whose predominant symptoms were: depressed mood, psychomotor retardation, loss of interest, feelings of guilt, insomnia, anorexia, and functional somatic complaints" (Ayd 1960, p. 320). In developing amitriptyline into an enormously successful product, Merck helped sell depression as a treatable disease (Healy 1997). To help sell depression, Merck bought and distributed 50,000 copies of Ayd's 1961 book, *Recognizing the Depressed Patient: With Essentials of Management and Treatment*. Written for the general practitioner, the book argues that depression is a ubiquitous disorder found not only in hospitals but also among outpatients. The use of rating scales, notably the Hamilton Depression Rating Scale, which defined depression using the same symptoms treated by imipramine and amitriptyline (Hamilton 1960), further instantiated depression as a real entity (although, as some have suggested, through a tautology).

3.4.2. Monoamine oxidase inhibitors. Released as an antidepressant at the same time as imipramine, iproniazid, the first MAOI, helped bolster the idea of depression as a nearly ubiquitous illness that could be treated with psychopharmacological agents. Largely because of the potential of MAOIs to precipitate a hypertensive crisis if one ingested food high in tyramine, they never attained the same widespread popularity achieved by the tricyclics. However, as with the previous drugs, researchers discovered the antidepressant properties of the MAOIs in a circuitous, serendipitous process. After World War II, Hoffman–LaRoche obtained large supplies of hydrazine, which had been used as a component of German rocket fuel. Using hydrazine, the company synthesized two drugs that they believed might have antituberculosis properties—isoniazid (Rimifon) and iproniazid (Marsilid)—and launched both in 1951 (Shorter 2008).

In 1952, Irving J. Selikoff and Edward Robitzek (Selikoff & Robitzek 1952) published their findings on the effectiveness of iproniazid and isoniazid in the treatment of tuberculosis. To their surprise, iproniazid had the side effect of elevating patients' mood. Five years later, Frank Ayd and George Crane separately reported that depressed tuberculosis patients became less depressed while on iproniazid. Nathan S. Kline was the first to report on iproniazid's effects on nontubercular depressed patients. Uncertain about the size of the market for drugs to treat depression, Hoffman–La Roche almost withdrew support from Kline, but ultimately continued support (López-Muñoz & Alamo 2009, p. 1567). By the end of the 1950s, three new MAOIs had been introduced: isocarboxazid (trade name Marplan; Hoffman–LaRoche), phenelzine (trade name Nardil; Warner Chilcott), and tranylcypromine (trade name Parnate; SKF).

3.4.3. Meprobamate and the benzodiazepines. The first genuine blockbuster psychiatric drug in terms of sales, the minor tranquilizer meprobamate, was synthesized in 1951 and then launched under the trade name Miltown in 1955. In 1946, working in Yorkshire, England, Frank Berger began studying mephenesin and discovered during animal testing that it caused sedation. Human testing showed that mephenesin also diminished anxiety and caused muscle relaxation. In 1951, at Wallace Laboratories in the United States, Berger succeeded in developing a longer-acting form of the compound (Shorter 2008). Four years later it was brought to market as Miltown (Wallace Laboratories) and Equanil (under license to Wyeth). Marketed for "anxiety, tension, and mental stress," sales of Miltown exceeded all expectations (Shorter 2008, p. 42). Since Wyeth had the larger sales force, Equanil outsold Miltown by a factor of three to one by 1960 (Tone 2008, pp. 72–73). Nevertheless, by 1965, more than 14 billion tablets of Miltown (amounting to about 500 million prescriptions) had been sold (Shorter 2008, p. 45).

Just as reports of meprobamate's addictive properties surfaced, the first marketed benzodiazepine, chlordiazepoxide (Librium), appeared. Leo Sternbach at Hoffmann–LaRoche hoped to create a novel new tranquilizer that would rival the success of Miltown, and, instead of modifying the molecular structure of a known antianxiety drug, he began screening unique molecular entities. He started with benzheptoxdiazines, based on his previous experience with the compounds and his belief that they might be biologically active, but he had no success in screening some 40 derivatives. One particular compound, labeled Ro 5-0690, was shelved when Sternbach was reassigned to work on antibiotics in 1956. In 1957, when cleaning up his lab, he sent the sample for testing rather than throwing it out. Animal testing proved it was a potent muscle relaxant that did not produce excessive sedation. In comparison to meprobamate, it was more potent, apparently safer, and produced less sedation. Hoffman–LaRoche received FDA approval for Librium in February 1960.

In synthesizing chlordiazepoxide, Sternbach inadvertently had created an entirely new class of chemicals, the benzodiazepines. He and his group would go on to synthesize and patent a number of new benzodiazepines, including flurazepam (Dalmane) and clonazepam (Klonopin). His most famous product, synthesized on October 26, 1959, was given the name diazepam (Valium). Released in 1963, Valium redefined the meaning of blockbuster drug. It became the most widely prescribed drug in the world between 1968 and 1981 and was the first drug in history to reach sales of more than $100 million (Tone 2008, p. 153).

3.5. Psychopharmacology in Context

Often the theory and practice of psychodynamic psychiatry and psychopharmacology are portrayed as contradictory, mutually exclusive activities and allegiances. In the 1970s, psychiatrists waged heated battles over the status of psychoanalytic knowledge, especially whether it would have a role in the 1980 revised edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III; Am. Psychiatr. Assoc. 1980). But, despite occasional skirmishes, the 1950s illustrate a symbiotic relationship between psychodynamic psychiatry and psychopharmacology. Paradoxically, although psychoanalysts had come to dominate the profession by the early 1950s, their influence on psychiatric science and practice contributed in no small measure to the spectacular success of psychopharmacology. Two particular points are worth noting this regard. First, largely driven by the psychoanalytic belief that there were no sharp divisions between the normal and the pathological, psychiatrists substantially enlarged the domain of the pathological, transforming many psychological ills that had previously been seen more as problems of daily living into an orbit of psychiatric diseases treatable by clinical modalities such as psychotropic drugs (Braslow & Starks 2005). Second, psychiatrists saw psychotropic drugs

not as alternatives to psychotherapy but as critical adjuncts to treatment, making it easier for the patient to participate in psychotherapy and the social world.

The changing epidemiology of patients in state hospitals illustrates the expanding domain of the pathological. We see a marked expansion of the kinds and numbers of patients admitted into state hospitals before and after World War II. Those admitted with nonpsychotic diagnoses in California increased from 1% in 1935 to 17% in 1960. This increase was not simply a reshuffling of diagnostic boundaries but, rather, a real expansion of legitimate objects of psychiatric treatment. In California, these nonpsychotic disorders included psychoneurosis, psychopathic personality, primary behavior disorders, sexual psychopathy, psychoneurotic reaction, personality pattern disturbance, personality trait disturbance, antisocial reaction, special symptom reaction, and transient situational personality disturbances (Starks & Braslow 2005).

The publication in 1952 of the first edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-I; Am. Psychiatr. Assoc. 1952) represented, in part, the growing influence of psychodynamic psychiatry and the lingering influence of Adolf Meyer, especially evident in the use of the word "reaction" to describe the major psychiatric diseases. Meyer believed that psychiatric diseases were the product of (or a "reaction to") a complex mix of biological, social, and psychological factors, the latter reflecting the repression of unconscious conflicts that, in turn, stemmed from complex past relationships and one's innate predispositions.

The importance of the dimensional perspective in the 1950s is reflected in the formal adoption of Eugen Bleuler's "schizophrenia" over Emil Kraepelin's "dementia praecox" in the DSM-I. Kraepelin believed that psychiatric diseases represented real, discrete, and bounded disease entities that were biologically rooted. In contrast, deeply influenced by psychoanalysis, Bleuler's conception of schizophrenia better accommodated (rightly or wrongly) American psychiatrists' growing infatuation with psychoanalysis and its dimensional view of illness.

Bleuler, a Swiss psychiatrist, first coined the term schizophrenia in 1908 and in 1911 published his most famous monograph, *Dementia Praecox or the Group of Schizophrenias* (Bleuler 1950). American psychiatrists began using the term interchangeably with dementia praecox in the 1920s, although Bleuler's monograph did not appear in English until 1950. As American psychiatry was increasingly influenced by psychoanalysis, schizophrenia became correspondingly a disorder with amorphous boundaries, shaped as much by personal history, social relationships, and psychological meaning as it was by biology. Thus, by reclassifying dementia praecox as "schizophrenic reaction" in the 1952 DSM-I, the American Psychiatric Association acknowledged what had already become fact, namely that even the most biological-appearing disease was a disorder that shaded from nearly normal (e.g., latent and simple schizophrenic reactions) to the overtly psychotic (e.g., schizophrenic reaction, paranoid type). Such a view also meant that psychotherapy remained the most effective intervention, with somatic treatments, drugs, and even ECT merely adjunctive to the psychotherapeutic process (Sadowsky 2016).

3.6. Psychopharmacology in Everyday Clinical Practice

Although outpatient care grew rapidly after the war, state hospitals continued to be a crucial part of American psychiatry well into the 1960s. The state hospital population peaked in 1955 at about 550,000 resident patients. At the same time, conditions within these institutions improved substantially as states, no longer constrained by the war effort, invested large sums in staff and in infrastructure. Despite a common misconception that state hospital psychiatrists were uninterested in their patients' psychodynamics, they often employed psychoanalytic concepts in understanding their patients. And they saw psychotropic drugs not as replacements for, but as important adjuncts to, psychological and social treatments.

We can see the influence of psychoanalytic thought clearly in the case of R. H., who was admitted to Stockton State Hospital in 1955. In his late teens he was diagnosed with schizophrenic reaction. The physician's diagnostic formulation placed the patient's illness within a psychodynamic framework. "The patient," the psychiatrist summarized, "is a third generation of Italian Catholic cultural heritage."

> The father appears to be very rigidly and aggressively domineering, and the mother appears to be a warm and loving, but ineffectual, parent. There appears to be a great deal of conscious and unconscious hostility between these parents….It is possible that the patient is torn between the desire to act out his father's hostility and the desire to be more positive or submissive like his mother.
>
> Official Diagnosis: Schizophrenic reaction.

As this short summary suggests, the physician deemed the patient's relationships with a "rigidly and aggressively domineering" father and his "warm and loving, but ineffectual" mother as central to making sense of the patient's schizophrenic reaction. Further, when it came to therapeutic recommendations, the psychiatrist believed that psychotherapy was necessary to help make conscious the unconscious conflicts that either led to or unmasked his psychotic illness. He also prescribed Thorazine but, as he made clear, it was not treating the core of the illness. Six months after admission, the psychiatrist observed: "The patient appears to be responding to Thorazine, reducing his agitated behavior. This is only an added effect. It is not affecting the components of his illness."

Reflecting, as well as shaping, clinical practice, pharmaceutical companies encouraged psychiatrists to use psychotropic drugs (including antipsychotics) as adjuncts to psychotherapy. This is illustrated (**Figure 1**) in an advertisement for Serpanray (reserpine, manufactured by Panray) that appeared in the 1956 *American Journal of Psychiatry*. We see a distraught-looking man seated in a desolate landscape. Just off to his side is a precipice. Behind him, a door is cracked slightly open with a sliver of light shining through. On the other side of the door is a lush landscape with trees, grass, and what appears to be a small town. The ad copy proclaims: "Opens the door to more successful psychotherapy…Ataractic Therapy for Neuro-Psychiatric Conditions."

From the beginning of the psychopharmacological revolution of the 1950s, psychiatrists held a variety of views on the usefulness of psychotropic drugs in the context of psychotherapy. At one extreme, some argued that psychotropic drugs completely interfered with psychotherapy. As one psychiatrist put it in 1956: "With regard to the use of the drugs on acute patients with a great deal of anxiety receiving psychotherapy, we have not used it because it allays the anxiety. The chap then has no reason for continuing psychotherapy, and so won't cooperate. Psychotherapy doesn't work with the drug" (Veterans Adm. 1956, p. 14). However, most claimed that psychotherapy and psychotropic drugs worked together synergistically (Sarwer-Foner 1960). Few would have foreseen a future in which psychotropic drugs would either devalue the importance of psychotherapy or, even more unimaginable, raise fundamental questions about the efficacy of psychotherapy.

4. FORGING DISEASE SPECIFICITY: 1964–1988

Between the mid-1960s and the late 1980s, American psychiatry underwent radical changes. In the 1950s, it was a profession dominated intellectually by psychoanalysis and clinically by massive state hospital systems. Hardly 20 years later, both state hospitals and psychoanalysis had all but faded away. The role of psychopharmacology in these changes is extremely complicated. We think these larger, macro-level changes in the profession both were shaped by and shaped developments in psychopharmacology. But we voice caution as to any causal assumptions in the story that follows.

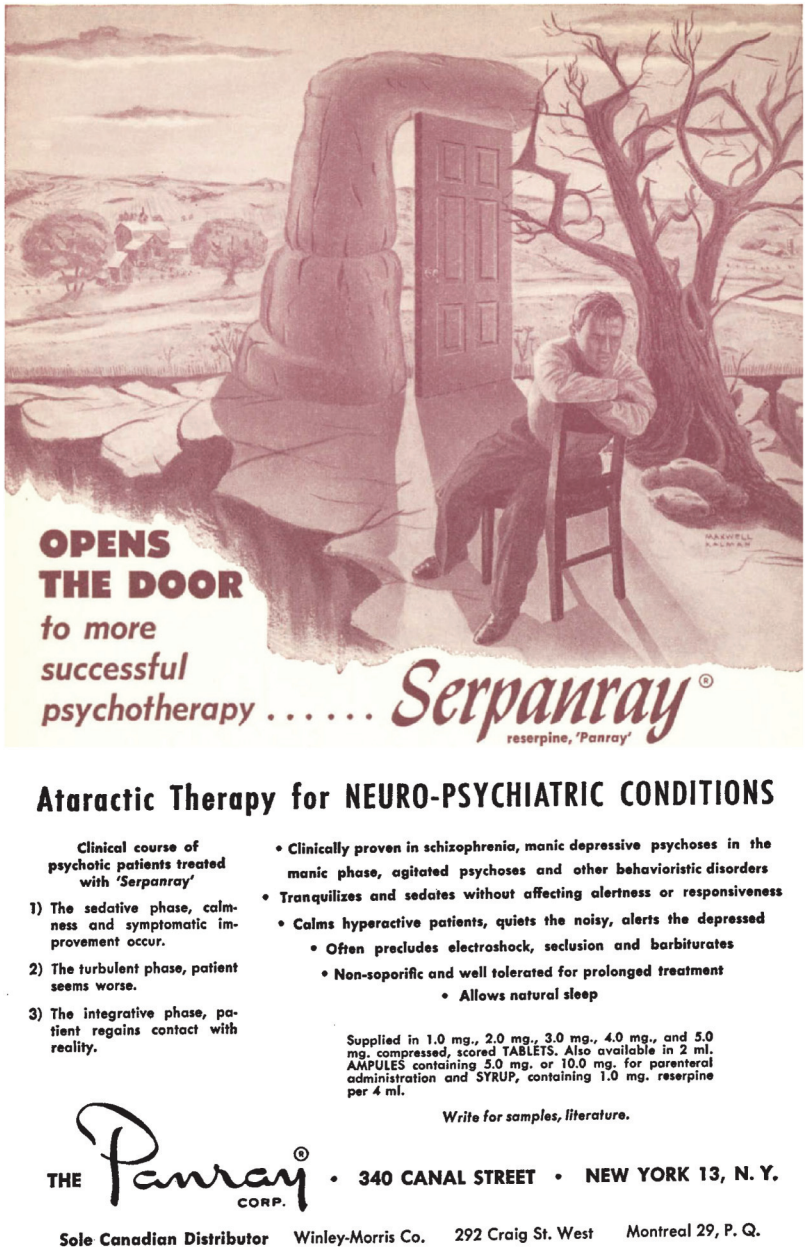

Figure 1

Serpanray advertisement from the *American Journal of Psychiatry* (Farrar 1956).

Larger political, economic, and cultural forces no doubt had the biggest roles in shaping psychiatry and psychopharmacology.

As clinical psychiatry moved out of state hospitals and psychoanalysis gave way to a more biologically informed psychiatry, psychopharmacology played a part in two major trends that occurred between the mid-1960s and late 1980s. First, the discovery of psychotropic drugs in the 1950s had a central role in the explosive growth of the neurosciences. Second, psychiatry discovered a new method for evaluating antipsychotics, namely the RCT. As we discuss below, the RCT played a critical part in moving psychiatrists and other clinicians away from the dimensional way of seeing disease to a more categorical vision of disease. We then look more closely at the ways in which changes in clinical care were shaped by the psychopharmacological revolution.

4.1. Creating Neuroscience

Without too much exaggeration, the psychopharmacological discoveries were indispensable to the creation of modern neuroscience and to our understanding of how neurons communicate with one another. Prior to the 1950s, most scientists believed that central nervous system (CNS) neurons communicated through electrical impulses. Neurochemical transmission had been recognized since 1933, when Henry Dale definitively showed that acetylcholine was a chemical messenger between synapses in the peripheral nervous system and at neuromuscular junctions, but its exact mechanism remained obscure. From the mid-1950s onward, as researchers uncovered the central role of chemical neurotransmitters in the CNS, psychopharmacological agents proved crucial. For example, in the late 1950s and early 1960s, Arvid Carlsson proved the central role of dopamine in the mechanism of action for phenothiazines, which become the basis for the dopamine hypothesis of schizophrenia.

Another neurotransmitter was isolated in 1948 from platelets and named serotonin because of its vasoconstriction properties and origins in serum. In 1952, Betty Twarog and John Welsh identified serotonin as a neurotransmitter present in mammalian brains. In 1953, John Gaddum discovered that LSD antagonized serotonin activity (Gaddum 1953). Given that LSD blocks serotonin in the brain and given that LSD causes psychotic symptoms, it was logical to hypothesize that serotonin is critical to sanity. In the same year, Dilworth Woolley and Elliott Shaw proposed a serotonin model of schizophrenia based upon similar logic: "[T]he suppression of its [serotonin] action results in mental disorder. In other words, it is the lack of serotonin which is the cause of the disorder" (Baumeister & Francis 2002, p. 267). In 1955, Bernard Brodie and colleagues at the US National Institute of Mental Health (NIMH) provided direct evidence for the physiological function of serotonin and showed that reserpine depleted serotonin from neuronal storage sites (Pletscher et al. 1955). In 1957, Carlsson and his colleagues further found that reserpine depleted the catecholamines epinephrine, norepinephrine, and dopamine, as well as serotonin (Carlsson 2001). They concluded that reserpine acted by nonspecifically blocking the storage of all monoamines, which are depleted by subsequent metabolic breakdown (Baumeister & Francis 2002).

Carlsson then showed that they could reverse the motor effects of reserpine-treated mice by giving the mice L-dopa, a metabolic precursor of dopamine but not of serotonin. This suggested the importance of dopamine over serotonin; yet the role of dopamine in the CNS was thought to be negligible (Carlsson et al. 1957). However, Carlsson and his colleagues suggested that dopamine was more than a precursor to the other catecholamines. Carlsson then demonstrated that dopamine mediated the effects of reserpine (Carlsson 2000). In a critical step toward understanding how antipsychotic drugs in general might act, researchers in the early 1960s demonstrated that dopamine was depleted in the autopsied brains of individuals with Parkinson's

disease and that the administration of L-dopa helped alleviate some of the motor symptoms of the disease.

The fact that reserpine and the phenothiazine drugs produced Parkinsonian symptoms and that there seemed to be a relationship between side effects and therapeutic efficacy strongly suggested that dopamine was involved in the mechanism of action for antipsychotic drugs. Yet the phenothiazines, similar to chlorpromazine, did not deplete dopamine storage. In 1963, Carlsson and Margit Lindqvist performed experiments with chlorpromazine and haloperidol and suggested that the drugs were blocking the catecholamine receptors rather than dopamine receptors specifically. However, during the following decade, researchers were able to show that antipsychotic drugs increased the concentration of dopamine brain metabolites, an effect directly proportional to antipsychotic potency. By the mid-1970s, scientists definitively demonstrated dopaminergic receptor blockade by directly measuring binding affinity (Baumeister & Francis 2002).

The dopamine hypothesis of schizophrenia (DHS) originated in the work of Carlsson and others on the mechanism of action of antipsychotics, and it has been the best known etiological theory of modern psychiatry, if not widely accepted, since the late 1970s. As Kenneth Kendler and Kenneth Schaffner compelling argue, the longevity of the DHS owes much to a conflation of the scientific evidence for the antipsychotic mechanisms with a theory of schizophrenia since little solid etiological evidence exists to support the DHS (Kendler & Schaffner 2011). According to Herbert Meltzer and Stephen Stahl in a 1976 *American Journal of Psychiatry* review of the hypothesis:

> In its simplest form, this hypothesis states that schizophrenia may be related to a relative excess of DA [dopamine]-dependent neural activity. It is derived from pharmacologic evidence that drugs that decrease DA activity (e.g., the phenothiazines) may be antipsychotic and drugs that promote DA activity (e.g., amphetamine) may be psychotomimetic. The particular means by which "too much dopamine" is produced in schizophrenia is not yet known. (Meltzer & Stahl 1976, p. 19)

The DHS has not survived the test of time unscathed. But it exerted a profound influence on subsequent neurobiological research, thus continuing efforts to understand how psychotropic drugs work, and on the growing belief in the categorical nature of psychiatric disease. In many ways, Meltzer and Stahl hit upon the fundamental problem in understanding psychiatric disorders by way of psychopharmacology: the mechanism by which a drug might work, such as by blocking dopamine, says little about the fundamental nature of the disease, such as "the particular means by which 'too much dopamine' is produced." Nevertheless, the conflation between mechanisms of action and theories of psychiatric disease has had a powerful role in the narrowing of psychiatric vision toward a more exclusively biological perspective.

Similarly, the monoamine hypothesis of depression is based upon the scientific understanding of how antidepressants work. In 1965, two articles appeared, one in the *American Journal of Psychiatry* by J.J. Schildkraut (1965) and the other in the *Archives of General Psychiatry* by William Bunney and John Davis (Bunney & Davis 1965). Both articles propose a catecholamine hypothesis of depression based upon similar evidence. Schildkraut summarizes the hypothesis as follows:

> This hypothesis, which has been designated the "catecholamine hypothesis of affective disorders," proposes that some, if not all, depressions are associated with an absolute or relative deficiency of catecholamines, particularly norepinephrine, at functionally important adrenergic receptor sites in the brain. (Schildkraut 1965, p. 509)

Similar to the dopamine hypothesis, the catecholamine hypothesis relied upon the effects of drugs, both clinically and in vitro. Some of the evidence Schildkraut assembles is as follows: MAOI drugs

increase levels of norepinephrine and serotonin in the brain in animals and are antidepressants in humans; amphetamine releases norepinephrine from neurons and blocks inactivation; acute administration of amphetamine causes rebound depression, presumably from depletion of norepinephrine; imipramine, desipramine, and amitriptyline inhibit the reuptake of norepinephrine into neurons.

Similar to the DHS, the catecholamine hypothesis exerted a profound effect on the ways in which psychiatric disease was understood and what counted as a legitimate intervention. In particular, these hypotheses suggest that psychotherapeutic approaches might be of secondary importance in the treatment of psychiatric disease.

4.2. The Randomized Controlled Trial

Although often neglected in the history of psychopharmacology, the RCT was as important in defining psychiatric illnesses and their treatment as were the psychopharmacological agents themselves. Propelled by the 1962 FDA amendment that pharmaceutical companies would have to prove efficacy as well as safety, the FDA made the RCT the sole arbiter of drug efficacy by the early 1970s. Not just a rigorous evaluation, the RCT has dramatically altered what counts as a scientific fact for clinical scientists. It dethroned the scientific importance of the individual case study and, instead, required scientists and clinicians to consider populations of patients, bias, measurable outcomes, and confounding factors. The RCT shifted the focus from the expertise of the individual clinician and the unique doctor–patient relationship toward an emphasis on results (most often quantitative) and interventions that could be replicated across clinicians, patients, space, and time. The RCT helped to dethrone psychoanalytic dominance and, at the same time, reinforced drug treatment and associated disease specificity.

The RCT is a relatively new invention. Prior to the mid-twentieth century, clinicians defined clinical science as expert opinion based upon a mix of historical case–controls, open trials, and clinical judgement. The origins of the clinical trial have been well documented (Armitage 1972, Lilienfeld 1982, Kaptchuck 1998). Most locate its formal birth in the United Kingdom's Medical Research Council's streptomycin trials that began in 1946 (Med. Res. Counc. 1948), but the basic elements that coalesced into this embryonic incarnation of the clinical trial—blinding, controls, randomization, and placebos—each have their separate histories (Marks 1997). In the 1940s and 1950s, after the introduction of lobotomy and the various shock therapies, psychiatrists began voicing concerns over the inadequacy of their methods for determining whether a treatment actually worked (Hoffman 1949, Bourne 1953, Jenkins & Holsopple 1953, Zubin 1953). Nearly all interventions used prior to the introduction of chlorpromazine failed when scrutinized with the RCT (Mermelstein 1956, Ackner et al. 1957, Casey et al. 1960).

Lithium, reserpine, and chlorpromazine were the first to be studied using the RCT (Healy 1997, p. 91). In one of the very first randomized trials, Joel and Charmian Elkes (1954) gave chlorpromazine to 27 patients drawn from what were known as the disturbed wards of the hospital at the University of Birmingham, United Kingdom, and cautiously concluded: "The reply to the question whether the drug may be useful in the management of the chronically overactive psychotic would thus appear to be qualified 'yes'" (Elkes & Elkes 1954, p. 564). They gave a more unqualified endorsement of the method they used: "The combination of the 'blind' nature of the trial, the fact that the patient was used as his own control, and agreement among the different observers, all contributed towards some confidence in a field in which assessment is notoriously difficult" (Elkes & Elkes 1954, p. 562). Schou et al. (1954) published the first RCT comparing lithium with placebo in patients with mania. Similar to the Elkes' study, they employed a crossover design. Davies & Shepherd (1955) from the Maudsley Hospital in London employed the first parallel group design in their study of reserpine in anxious and depressed patients.

Yet the RCT was not without its critics, notably psychodynamic psychiatrists, who argued that the RCT ignored many factors, such as the doctor–patient relationship. In an article aptly titled "The fallacy of the 'double blind,'" Joseph Barsa (1963) expressed a commonly held conviction:

> It is not possible to gain a valid evaluation of a drug and eliminate the clinical skill and judgement of the investigator. It is erroneous to believe that treatment with a certain drug will have the same result, no matter who the therapist is….
>
> Yet, despite all these deficiencies of the 'double blind' it is still proposed as the method of choice in the investigation of psychotropic drugs….However, instead of bringing clarity, the "double blind" has only succeeded in adding to the confusion by many half-truths and unwarranted conclusions. (Barsa 1963, p. 1175)

History was not on Barsa's side. The FDA, under political pressure to define a standard for drug efficacy that would mediate clinical controversies and override the claims of litigious pharmaceutical companies, enshrined the RCT in 1970 as the single most important arbiter of what counts as clinical scientific evidence. The well-funded manufacturers responded by perfecting the use of the RCT as a marketing tool and ensuring its dominance as a standard for therapeutic efficacy.

All scientific methods carry assumptions about the nature of the world; methods shape both the questions that can be asked and the answers that can be extracted from nature. The RCT lends itself to a bacteriological model of disease in which illnesses are discrete entities, isolatable from their sociocultural and psychological context. Because treatment outcomes must be measurable within RCTs, they are separable from the meanings patients give to the treatment and the doctor–patient relationship. Thus, the RCT reinforces a reductionist model of psychiatric disease that mirrors bacteriological perspectives: one in which illnesses are discrete, biological entities without individual or sociodynamic context.

From the early 1960s to the late 1980s, no new antipsychotic drugs appeared; yet psychopharmacology helped to radically refashion our understanding of mental illness. While the dramatic strides in neurobiological understanding helped to affirm the belief that the drugs treated discrete biological diseases, the RCT helped to crystallize the major disease categories in psychiatry for which successful treatment requires not only interventions that can be evaluated with RCTs but also diseases defined by symptoms that the interventions (the drugs) can treat.

In 1964, Jonathan Cole and his colleagues (Cole et al. 1964) published the findings of an important multicenter RCT conducted at nine different sites. Funded by the NIMH and one of the most widely cited in psychiatry and a model for subsequent trials, this study provided definitive proof of the efficacy of phenothiazine in the treatment of schizophrenia. The researchers randomized 463 patients to four different treatments: chlorpromazine, fluphenazine, thioridazine, or placebo; they found that patients on phenothiazines did significantly better than those on placebo. The authors concluded: "The findings of this study support the view that phenothiazine drugs have a generalized antischizophrenic effect and are useful in patients suffering from acute schizophrenia psychoses" (Cole et al. 1964, p. 260), thus reifying the observed effects of the compounds as definitive of the disease they sought to treat.

4.3. Narrowing Clinical Responsibility

State hospital populations peaked in 1955, coinciding with the widespread introduction of chlorpromazine and reserpine. At first, many attributed the subsequent fall to the effect of the newly introduced psychotropic drugs (Brill & Patton 1957, 1959, 1962). Over time, scholars increasingly questioned the causal relationship between the introduction of antipsychotic drugs and the drop

in populations in state hospitals (Gronfein 1985, Pow et al. 2015). The historian and sociologist of psychiatry, Andrew Scull (1990), best summarizes the complex factors that emptied state hospitals:

> The mental hospital census, having declined slowly between 1955 and 1965, dropped precipitously over the next two decades—not primarily, as some have alleged, because phenothiazines provided a technological fix for the psychosis, but rather in response to a broad expansion of social welfare programs, growing fiscal pressures on the states, and the opportunity to transfer costs away from the state budget, helped along, in a more minor key, by the interventions of public interest lawyers who sought to make it more difficult to employ the police power of the state to compel the mentally ill to enter psychiatric treatment facilities. (Scull 1990, p. 307)

As the hospitals emptied, psychiatrists became increasingly reliant on psychotropic drugs, no longer as adjuncts but as the main treatment. Deinstitutionalization led to both increasingly shorter hospital stays and, up through the 1970s, rising admission rates. As psychiatrists had less and less time to spend with their patients and had fewer and fewer resources to marshal in their treatment, they had little choice but to focus on the rapid elimination of symptoms in order to hasten discharge.

Psychopharmacology's impressive success also sowed seeds of discontent. Psychotropic drugs were clearly not curative, even if they dramatically quelled agitated behavior and diminished, but did not eliminate, the most overt psychotic symptoms. Researchers found it difficult to demonstrate clinically significant improvement, especially over the long term. Most alarmingly, antipsychotic drugs posed a number of significant side effects. One, in particular, vividly marks its sufferer. A movement disorder that appears after long-term use of antipsychotic drugs, tardive dyskinesia entails involuntary movements of the lips, tongue, face, arms or legs, or some combination of these. It is difficult to reverse, even after the cessation of antipsychotic drugs. By the 1970s, it had become a major concern as researchers discovered that the prevalence was significantly higher than had originally been thought (Freeman 1973, Baldessarini et al. 1980, Gelman 1999).

Just as disconcerting was the failure of psychotropic drugs to solve the problems wrought by deinstitutionalization. Regardless of the impact of antipsychotic drugs in emptying state hospitals, they did little to solve the problems that those with severe mental illness faced when no longer able to find solace in the asylum. From the 1970s onward, individuals with severe mental illness were at increasing risk of homelessness and incarceration as state hospitals contracted in size. From 1960 to 1969, the population of residents in state hospitals decreased by 31%. During the next 5 years, the resident population plummeted more than twice as rapidly as it had during the previous 10 years. In 1974, the resident population was at 215,573, down by 61% from its 1955 high of 558,922 (Kramer 1977). It did not go unnoticed that deinstitutionalization simultaneously created growing populations of homeless mentally ill people and incarcerated mentally ill people, facts that underlined that psychotropic drugs were not the hoped-for panacea for those suffering from severe mental illness.

5. HOPE AND ITS DISCONTENTS: LATE 1980s TO THE PRESENT

The future for psychopharmacology did not look bright in the early 1980s. Despite the publication of DSM-III, there had been scant clinical progress in psychiatry in regard to psychopharmacology. No fundamentally new drug had entered the scene for more than two decades, and the enthusiastic hopes that technological solutions in the guise of psychopharmacology would solve the problems of severe mental illness had been cruelly dashed by the reality of the collapsing American welfare state and the fragmentation of public services. Yet hope for a pharmacological solution again

surfaced, although from an unlikely source, in that it came from the rediscovery of a drug that had first been synthesized in the late 1950s.

5.1. Rediscovery of Clozapine and Atypical Antipsychotic Drugs

In 1958, the Swiss pharmaceutical company Wander had synthesized a series of new tricyclic compounds, including clozapine, the only antipsychotic that produces virtually no tardive dyskinesia and Parkinson-like side effects.

The early history of clozapine did little to suggest its later major importance (Hippius 1989, 1999, Crilly 2007). Early animal and human testing presented mixed and anomalous results. One trial failed to demonstrate an antipsychotic effect while another trial succeeded. Later human trials in the 1960s demonstrated that clozapine was not only effective in treating psychotic symptoms but also that it did not produce the motor side effects that invariably accompanied the then-existing effective antipsychotic drugs. The absence of motor side effects and tardive dyskinesia perplexed researchers, given the belief that motor side effects were necessary concomitants of drug efficacy. Clozapine's defiance of this conventional belief led researchers to designate it as atypical.

When applied in the 1960s, the adjective atypical had a modest, primarily descriptive, meaning and did little to promote the use of clozapine. In 1975, eight patients in Finland died of agranulocytosis (the inability of the bone marrow to make sufficient white blood cells) while taking clozapine, which led Sandoz (the pharmaceutical company that had taken over Wander) to halt development efforts. Nevertheless, increasing concerns over tardive dyskinesia, and a suspicion that clozapine might be more effective than other antipsychotic drugs, kept a few embers of interest in the drug alive. Beginning in 1984, Sandoz conducted a multicenter study that demonstrated the superior efficacy of clozapine over chlorpromazine in patients previously unresponsive to antipsychotic drugs (Kane et al. 1988, 1989). Sandoz also instituted a system of mandatory blood monitoring in patients taking clozapine so that the medication could be stopped if white blood cell counts began to drop, thereby preventing the onset of agranulocytosis. In 1990, the FDA gave final approval for the exclusive marketing of clozapine.

Not unlike the 1964 US NIMH study led by Cole, this study had profound effects on the field of psychopharmacology in general and the treatment of psychotic disorders in particular. It affirmed the growing skepticism that dopamine blockade (especially of the D2 receptors) was a necessary ingredient for antipsychotic efficacy in light of the continued failures to identify dopamine abnormalities postmortem in patients with schizophrenia. The fact that clozapine did not appreciably block D2 receptors and had no motor side effects further imperiled the dopamine hypothesis and, from the 1970s onward, led pharmaceutical companies to use clozapine, with its higher affinity for serotonergic rather than dopaminergic receptors, as a new model for drug development.

Such reasoning led Janssen Pharmaceuticals to the synthesis of risperidone in 1984. The company obtained FDA approval in 1993 to market it as Risperdal. Janssen enthusiastically embraced the term atypical, and risperidone become the first new atypical antipsychotic drug marketed in the United States. In 1996, Eli Lilly brought to market the atypical antipsychotic drug olanzapine (brand name Zyprexa). A year later, the FDA approved AstraZeneca's quetiapine (brand name Seroquel). Eight additional atypical antipsychotic drugs have entered the US market since 2000, including such widely prescribed compounds as aripiprazole in 2002 (trade name Abilify; Otsuka Pharmaceutical and Bristol-Myers Squibb), paliperidone in 2006 (trade name Invega; Janssen), and lurasidone in 2010 (brand name Latuda; Sumitomo Dainippon Pharma).

Throughout much of the 1990s and early 2000s, these drugs were hailed as major advances, fundamentally better than the first generation of antipsychotic drugs. Certainly, classification of

these new drugs as atypical helped, distancing them from the drugs developed in the 1950s and 1960s and the widespread disappointment that clung to them as long-term outcomes failed to improve (Insel 2010) and side effects increased. Also, neuroreceptor mythology, related to the activity of risperidone and others at 5-HT2A receptors, helped to reinforce the hope, if not the belief, that they were a fundamental advance. Some of the new drugs do, in fact, have great relative affinity for 5-HT2A receptors, although this is not universally characteristic of all second-generation agents. Pharmaceutical companies heavily promoted atypicals as more effective and safer than the first generation of antipsychotic drugs, especially for social withdrawal and cognitive deficits, core symptoms of schizophrenia that were untouched by first-generation antipsychotic drugs. The claims of safety did not hold up to scrutiny (see Section 5.4) as severe metabolic disturbances became apparent. It is likely (although not certain) that atypicals cause fewer movement disorders than do the first-generation drugs. Clozapine, however, remains the only antipsychotic that is virtually free from these side effects.

5.2. Better than Well: The Rise of the SSRIs

At the same time as the pharmaceutical industry looked toward developing novel antipsychotic drugs, they also turned their attention toward developing new antidepressants. Serotonin and its role in mental illness had been of interest ever since the 1950s. In 1954, John Gaddum, after accidentally ingesting LSD, which was already known to block serotonin, discovered that it had strong psychotropic effects, describing being "out of his mind for forty-eight hours" (Shorter 2008, p. 69). Then, in 1957, Bernard Brodie demonstrated that reserpine depleted neuronal stores when given to rabbits, which appeared to behave in a depressed manner, consistent with previous reports that some human patients became severely depressed when taking reserpine (Brodie & Shore 1957). However, interest in the role of serotonin was eclipsed after 1961 by Julius Axelrod et al.'s (1961) discovery that imipramine inhibited the reuptake of norepinephrine but not serotonin in neurons. Yet some researchers maintained an interest in serotonin and its possible role in depressive states, and in 1974, researchers at Eli Lilly developed a molecule that selectively blocked the reuptake of serotonin (Hillhouse & Porter 2015). This molecule was named fluoxetine, and Eli Lilly received FDA approval in 1987 to market it as an antidepressant under the trade name Prozac. Prozac was launched in 1988.

Other SSRIs quickly followed: sertraline (trade name Zoloft; Pfizer) in 1991, paroxetine (trade name Paxil; GlaxoSmithKline) in 1992, and citalopram (trade name Celexa; Allergan) in 1998. In contrast to older drugs for depression, fluoxetine was relatively easy to administer because of its side effect profile. As a result, patients with milder depressions appeared to benefit, and treatment could often be managed in primary care settings. Because of the apparent ease of prescription, the companies heavily marketed these drugs to primary care clinicians and consumers. Although unsupported by anything more substantial than clinical anecdote, Prozac achieved an almost mythic status as capable of making one even better than well. Emblematic of the hype that surrounded Prozac, Peter Kramer's *Listening to Prozac* claimed that Prozac possesses the ability to fundamentally remake personality and, as such, raises fundamental questions about the nature of the self (Kramer 1994). Irrespective of the thin evidence upon which such assertions rested, *Listening to Prozac* and the hubbub surrounding the first major psychotropic blockbuster since Valium generated a deep popular belief that the SSRIs represented a fundamental advance.

5.3. Pharmaceutical Profits and Psychotropic Drugs

Both the atypical antipsychotics and SSRI antidepressants produced spectacular profits for the pharmaceutical industry. The industry revived a moribund sector that had not marketed a

fundamentally new drug for more than two decades and, in a matter of just a few years, not only completely conquered the existing markets for antipsychotic and antidepressant drugs but also forged new ones. In the case of atypicals, although they were initially approved only for the treatment of schizophrenia, off-label use grew rapidly as the illusion of safety and efficacy encouraged physicians to prescribe atypicals for a variety of psychological ills, ranging from insomnia, anxiety, depression, and dementia to a host of childhood disorders. By the early 2000s, patients with bipolar disorder, depression, and dementia overtook patients with schizophrenia as the largest market for atypicals (Olfson et al. 2015). In expanding market share at the expense of the first generation, the pharmaceutical industry heavily marketed these agents as not only being safer and having fewer motor side effects but also as being more efficacious.

The launch of Risperdal in 1993 inaugurated a transformation of the market for antipsychotic drugs that produced previously unimaginable profits. On the eve of Risperdal's introduction, worldwide sales of antipsychotic drugs amounted to less than a billion dollars, with clozapine, the only marketed atypical, accounting for only a small fraction of this sum. During the next decade, atypical antipsychotic drugs captured more than 90% of the market, and worldwide sales of these compounds mushroomed to more than $10 billion. By 2011, sales of antipsychotic drugs topped $28 billion, becoming the fifth largest–selling drug class, just behind oncologics, respiratory agents, antidiabetics, and lipid regulators. The US pharmaceutical market accounted for the majority of these expenditures (as it does for the majority of pharmaceutical classes). Of the $28 billion spent on antipsychotic drugs in 2011, expenditures in the United States accounted for 64% of the total or $18.2 billion (**https://www.iqvia.com/**).

Companies were similarly successful in selling SSRIs. They handily conquered market share over the tricyclics and expanded into entirely new populations, including people diagnosed with obsessive–compulsive disorder, panic disorder, generalized anxiety disorder, social anxiety disorder, posttraumatic stress disorder, and premenstrual dysphoric disorder. In addition, the perceived safety of these compounds led to an increase in the use of antidepressants in children and adolescents. Prior to the introduction of fluoxetine in 1988, 40 million Americans were treated with an antidepressant, whereas 264 million received an antidepressant in 2011. A national survey conducted from 2009 to 2010 found that 10.4% of adults were taking an antidepressant. Moreover, these medications were most commonly being prescribed by primary care providers (Mojtabai & Olfson 2014).

5.4. A Darker Side

Just as the profits of SSRIs soared, a number of major problems emerged. Researchers began questioning the efficacy of SSRIs (Kirsch 2010, Wang et al. 2018). In 2003, the FDA issued an advisory that there was an increased risk for suicide in pediatric patients prescribed antidepressants. This was followed by warnings that both adults and children prescribed antidepressants should be monitored for suicidal behavior. In 2004, the FDA required a black box warning for all antidepressants stating that there was increased risk of suicidality in children, adolescents, and young adults. Before the FDA advisory, the rates of pediatric depression had been steadily rising. Following the advisory, there was both a decline in the diagnosis of depression in children, adolescents, and young adults and a decrease in the prescribing of antidepressants for these groups (Libby et al. 2007). Although the FDA advisory focused on children and adolescents, there was also a decline in the diagnosis of depression in adults (Valuck et al. 2007).

The atypical antipsychotic drugs encountered similar difficulties. The enthusiastic appraisals that the atypicals were more efficacious than the first generation did not hold up to close scrutiny. Clozapine remains the only atypical antipsychotic drug with proven superior efficacy over the

older drugs. Published in 2005 and 2006, two studies have proven to be especially influential demonstrations that atypicals, as a class, offer few advantages over the older drugs. One study, funded by the NIMH, compared a number of second-generation antipsychotics with perphenazine, an older drug (Lieberman et al. 2005). Although side effects differed among the drugs, there was no clear indication that perphenazine was less effective than the newer drugs. A 2006 study compared atypical with first-generation antipsychotic drugs in 14 sites across the United Kingdom. The researchers concluded that "there is no disadvantage across 1 year in terms of quality of life, symptoms, or associated costs of care" in using the first-generation antipsychotics compared with the non-clozapine atypicals (Jones et al. 2006, p. 1086). More recently, meta-analyses comparing antipsychotics have not found an efficacy advantage for newer drugs (Leucht et al. 2013).

None of the new drugs has been able to mimic clozapine's virtual absence of extrapyramidal side effects and tardive dyskinesia. They all produce some degree of motor side effects, although perhaps less often than first-generation drugs. At the same time, these newer drugs produce a variety of metabolic side effects that are as serious, if not more so, than those that plagued the first generation of antipsychotics. Significant weight gain, diabetes, and hyperlipidemia (elevated levels of lipids in the bloodstream associated with heightened risk of cardiovascular disease) are common side effects, although each of the newer antipsychotic drugs varies in the extent to which it produces these side effects. Nevertheless, these effects are not a defining characteristic of the newer antipsychotics. These effects had been noted in patients treated with clozapine as well as with first-generation antipsychotics. Antipsychotics such as ziprasidone and lurasidone have relatively small risks for these effects.

A darker side of pharmaceutical industry practices has been laid bare in a number of landmark lawsuits regarding the atypicals. Eli Lilly, Pfizer, AstraZeneca, Bristol-Myers Squibb, and Johnson & Johnson have been charged with or investigated for health-care fraud. In 2007, Bristol-Myers Squibb paid $515 million to settle allegations that the company had promoted Abilify (aripiprazole) for use in children and to treat dementia. In 2009, Eli Lilly paid $1.4 billion to settle allegations that it marketed Zyprexa (olanzapine) for a variety of unapproved uses. In the same year, Pfizer settled a major suit for the illegal marketing of Geodon (ziprasidone), and in 2010, AstraZeneca paid $520 million for the illegal marketing of Seroquel (quetiapine).

In retrospect, atypicality has served as much as a marketing tool as it has a legitimate description of a differently acting class of antipsychotic drugs. The term atypical increasingly has lost its meaning as we learn more about the efficacy and side effects of these drugs. After all, other than clozapine, all antipsychotic drugs (new and old) have nearly equivalent efficacy; all produce nasty side effects, some potentially fatal; and none works nearly as well as clinicians and patients wish it did.

Finally, a worrisome trend that bodes ill for future drug development is that a number of large companies recently either have closed their divisions for neuroscience drug development or substantially limited their investment in it. The industry has based this retreat on an expectation that development costs will not be offset by future profits. Ironically, fueled by the antipsychotic and antidepressant drug markets, the pharmaceutical industry has reaped enormous profits from psychotropic drugs. For example, between 1997 and 2001, US sales of psychotropic drugs increased by 24% per year (Mark et al. 2012). When considering total expenditures for mental health care, this growth comes at a cost in that expenditures for other components of care have not increased proportionally. During the same period, the amount of the total expenditure on mental health care increased from 14% to 23%. In 2012, the total amount spent in the United States on psychotropic drugs was $57.8 billion (of which, antidepressants accounted for $17.8 billion and antipsychotics accounted for $17.6 billion). Psychotropic drugs made up 21% of the total spent on all pharmaceuticals (Hodgkin et al. 2016).

However, the rate of growth for psychotropic drugs has declined steadily since 2001—largely due to market saturation, declining drug prices, and loss of patent protection—with the associated influx of generics. While not necessarily in the public interest, the decision to shift research and development resources to other diseases likely makes business sense. Looking back, the drugs introduced since Prozac have reaped unimaginably huge profits despite being only marginally better than the drugs they have replaced. Perhaps pharmaceutical executives have made a calculated gamble that lightning usually does not strike twice.

6. CONCLUSIONS

Stepping back, the history of psychopharmacology and, indeed, the entire history of psychiatry look a bit like Sisyphus repeatedly pushing an enormous boulder up a hill only to have it come crashing back down just as it nears the crest. Psychiatrists keep believing that they are on the verge of radical breakthroughs in the care and treatment of mental illness only to have their hopes dashed by the reality of the enormous complexities of interactions between human psychological life, the brain, and the social world. Psychiatry and American culture have been particularly seduced by the technological solutions promised by a magic bullet that will simultaneously cure madness and provide simple explanations for the inexplicable. Psychopharmacological solutions have been especially compelling during the past 50 years since they require far fewer questions of how America cares for those unable to care for themselves.

One might despair. But we believe that this history is actually a hopeful one if we take seriously the lessons it has to teach us about the nature of mental illness. It is not that psychopharmacology has failed. Instead, we have failed our patients by adopting a myopia that sees only symptoms and their alleviation by psychoactive drugs. This narrowing of vision has been aided and abetted by a fraying social safety net and fragmented health-care system in which drugs increasingly are all psychiatrists feel they can offer their patients. But the failures of antipsychotic drugs, for example, to miraculously solve the consequences of deinstitutionalization teach us the enormously important lesson that mental illness, by definition, is a disease of the biological, psychological, and social.

During the past several decades, there has been a concerted effort in the care of patients with severe mental illness to instill hope that they are not fated to a life of disability. For our patients, we do not believe that biology is destiny. The history of psychopharmacology reminds us of that fact. While helpful, psychotropic drugs cannot and will not (at least for the foreseeable future) by themselves adequately treat the ravages of mental illness. Although we do not advocate a return to the past, we do believe that we have much to learn from that innocent world before the psychopharmacological era during which there was more to patients than simply symptoms and drugs taken to treat those symptoms.

DISCLOSURE STATEMENT

J.T.B. has no affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review. S.R.M. has served on advisory boards or been a consultant for a number of pharmaceutical companies including Janssen Pharmaceuticals, Eli Lilly, Lundbeck, Allergan, Otsuka Pharmaceutical, and Sunovion Pharmaceuticals. He has also served on advisory boards for the US Food and Drug Administration.

ACKNOWLEDGMENTS

The authors thank Kenneth Kendler, Kelsey C. Martin, and Marcia Meldrum for reading and critiquing versions of the manuscript. This work was supported by National Institute of

Mental Health grant 1R01MH080671 (to J.T.B.), who also received an Investigator Award in Health from the Robert Wood Johnson Foundation.

LITERATURE CITED

Ackerknecht EH. 1979. The history of the drug treatment of mental diseases. *Trans. Stud. Coll. Physicians Phila.* 1:161–70

Ackner B, Harris A, Oldham AJ. 1957. Insulin treatment of schizophrenia; a controlled study. *Lancet* 272:607–11

Am. Psychiatr. Assoc. 1952. *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: Am. Psychiatr. Publ. 1st ed.

Am. Psychiatr. Assoc. 1980. *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: Am. Psychiatr. Publ. 3rd ed.

Anton-Stephens D. 1954. Preliminary observations on the psychiatric uses of chlorpromazine (Largactil). *J. Ment. Sci.* 100:543–57

Armitage P. 1972. History of randomised controlled trials. *Lancet* 299:1388

Axelrod J, Whitby LG, Hertting G. 1961. Effect of psychotropic drugs on the uptake of H^3-norepinephrine by tissues. *Science* 133:383–84

Ayd FJ Jr. 1960. Amitriptyline (Elavil) therapy for depressive reactions. *Psychosomatics* 1:320–25

Ayd FJ Jr. 1961. *Recognizing the Depressed Patient: With Essentials of Management and Treatment*. New York: Grune & Stratton

Baldessarini RJ, Cole JO, Davis JM. 1980. Tardive dyskinesia: summary of a task force report of the American Psychiatric Association. *Am. J. Psychiatry* 137:1163–72

Barsa JA. 1963. The fallacy of the "double blind." *Am. J. Psychiatry* 119:1174–75

Baumeister AA, Francis JL. 2002. Historical development of the dopamine hypothesis of schizophrenia. *J. Neurosci.* 11:265–77

Benson WM, Schiele BC. 1962. *Tranquilizing and Antidepressive Drugs*. New York: Thomas

Bleuler E. 1950 (1911). *Dementia Praecox or the Group of Schizophrenias*. New York: Am. Inst. Psychol. Res.

Bourne J. 1953. The insulin myth. *Lancet* 2:964–68

Bower WH. 1954. Chlorpromazine in psychiatric illness. *N. Engl. J. Med.* 251:689–92

Braslow JT. 1997. *Mental Ills and Bodily Cures: Psychiatric Treatment in the First Half of the Twentieth Century*. Berkeley, CA: Univ. Calif. Press

Braslow JT, Starks SL. 2005. The making of contemporary American psychiatry, Part 2: Therapeutics and gender before and after World War II. *Hist. Psychol.* 8:271–88

Brill H, Patton RE. 1957. Analysis of 1955–1956 population fall in New York State mental hospitals in first year of large-scale use of tranquilizing drugs. *Am. J. Psychiatry* 114:509–17

Brill H, Patton RE. 1959. Analysis of population reduction in New York State mental hospitals during the first four years of large-scale therapy with psychotropic drugs. *Am. J. Psychiatry* 116:495–508

Brill H, Patton RE. 1962. Clinical–statistical analysis of population changes in New York State mental hospitals since introduction of psychotropic drugs. *Am. J. Psychiatry* 119:20–35

Brodie BB, Shore PA. 1957. A concept for a role of serotonin and norepinephrine as chemical mediators in the brain. *Ann. N. Y. Acad. Sci.* 66: 631–42

Bunney WE, Davis JM. 1965. Norepinephrine in depressive reactions: a review. *Arch. Gen. Psychiatry* 13:483–94

Carlsson A. 2000. *A Half-Century of Neurotransmitter Research: Impact on Neurology and Psychiatry*. Stockholm: Nobel Found.

Carlsson A. 2001. A paradigm shift in brain research. *Science* 294:1021–24

Carlsson A, Lindqvist M, Magnusson T. 1957. 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. *Nature* 180:1200

Casey JF, Lasky JJ, Klett CJ, Hollister LE. 1960. Treatment of schizophrenic reactions with phenothiazine derivatives: a comparative study of chlorpromazine, triflupromazine, mepazine, prochlorperazine, perphenazine, and phenobarbital. *Am. J. Psychiatry* 117:97–105

Cole JO, Goldberg SC, Klerman GL. 1964. Phenothiazine treatment in acute schizophrenia. *Arch. Gen. Psychiatry* 10:246–61

Crilly J. 2007. The history of clozapine and its emergence in the US market: a review and analysis. *Hist. Psychiatry* 18:39–60

Davies DL, Shepherd M. 1955. Reserpine in the treatment of anxious and depressed patients. *Lancet* 266:117–20

Drapes T. 1889. Hyoscin in insanity. *BMJ* 1:942

Elkes J, Elkes C. 1954. Effect of chlorpromazine on the behaviour of chronically overactive psychotic patients. *BMJ* 2:560–65

Farrar CB, ed. 1954. *Am. J. Psychiatry* 110(11)

Farrar CB, ed. 1956. *Am. J. Psychiatry* 112(12)

Freeman DX. 1973. Neurological syndromes associated with antipsychotic drug use: a special report. *Arch. Gen. Psychiatry* 28:463–67

Gaddum JH. 1953. Antagonism between lysergic acid diethylamide and 5-hydroxytryptamine. *J. Physiol.* 121:15P

Gelman S. 1999. *Medicating Schizophrenia: A History*. New Brunswick, NJ: Rutgers Univ. Press

Grob GN. 1994. *The Mad Among Us: A History of the Care of America's Mentally Ill*. New York: Simon & Schuster

Gronfein W. 1985. Psychotropic drugs and the origins of deinstitutionalization. *Soc. Probl.* 32:437–54

Hamilton M. 1960. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 23:56–62

Hall M. 1999. 'You have to get help:' frightening experience now a tool to help others. *USA Today*, May 7, p. A1

Healy D. 1997. *The Antidepressant Era*. Cambridge, MA: Harvard Univ. Press

Healy D. 2002. *The Creation of Psychopharmacology*. Cambridge, MA: Harvard Univ. Press

Healy D, Savage M. 1998. Reserpine exhumed. *Br. J. Psychiatry* 172:376–78

Hillhouse TM, Porter JH. 2015. A brief history of the development of antidepressant drugs: from monoamines to glutamate. *Exp. Clin. Psychopharmacol.* 23:1–21

Hippius H. 1989. The history of clozapine. *Psychopharmacology* 99(Suppl.):S3–5

Hippius H. 1999. A historical perspective of clozapine. *J. Clin. Psychiatry* 60(Suppl. 12):22–23

Hodgkin D, Thomas CP, O'Brien PL, Levit K, Richardson J, et al. 2016. Projected spending on psychotropic medications 2013–2020. *Adm. Policy Ment. Health* 43:497–505

Hoffman J. 1949. Critique of lobotomy. *N. Engl. J. Med.* 241:233–36

Insel TR. 2010. Rethinking schizophrenia. *Nature* 468:187–93

Jenkins RL, Holsopple JQ. 1953. Criteria and experimental design for evaluating results of lobotomy. *Res. Publ. Assoc. Nerv. Ment. Dis.* 31:319–27

Jones PB, Barnes TRE, Davies L, Dunn G, Lloyd H, et al. 2006. Randomized controlled trial of the effect on quality of life of second- versus first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch. Gen. Psychiatry* 63:1079–87

Kane JM, Honigfeld G, Singer J, Meltzer H. 1988. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch. Gen. Psychiatry* 45:789–96

Kane JM, Honigfeld G, Singer J, Meltzer H. 1989. Clozapine for the treatment-resistant schizophrenic: results of a US multicenter trial. *Psychopharmacology* 99(Suppl.):S60–63

Kaptchuck TJ. 1998. Intentional ignorance: a history of blind assessment and placebo controls in medicine. *Bull. Hist. Med.* 72:389–433

Kendler KS, Schaffner KF. 2011. The dopamine hypothesis of schizophrenia: an historical and philosophical analysis. *Philos. Psychiatry Psychol.* 18:41–63

Kerner J, McCoy B. 2017. *Antipsychotics: History, Science, and Issues*. Santa Barbara, CA: Greenwood

Kinross-Wright V. 1954. Chlorpromazine—a major advance in psychiatric treatment. *Postgrad. Med.* 16:297–99

Kirsch I. 2010. *The Emperor's New Drugs: Exploding the Antidepressant Myth*. New York: Random House

Kline NS. 1954. Use of *Rauwolfia serpentina* Benth. in neuropsychiatric conditions. *Ann. N. Y. Acad. Sci.* 59:107–32

Kramer M. 1977. *Psychiatric Services and the Changing Institutional Scene, 1950–1985*. Rockville, MD: NIMH (Natl. Inst. Ment. Health)
Kramer PD. 1994. *Listening to Prozac: A Psychiatrist Explores Antidepressant Drugs and the Remaking of the Self*. New York: Penguin
Kuhn R. 1958. The treatment of depressive states with G 22355 (imipramine hydrochloride). *Am. J. Psychiatry* 115:459–64
Kurland AA. 1955. Chlorpromazine in the treatment of schizophrenia: a study of 75 cases. *J. Nerv. Ment. Dis.* 121:321–29
Lehmann HE. 1955. Therapeutic results with chlorpromazine (Largactil) in psychiatric conditions. *Can. Med. Assoc. J.* 72:91–99
Lehmann HE. 1993. Before they called it psychopharmacology. *Neuropsychopharmacology* 8:291–303
Leucht S, Cipriani A, Spineli L, Mavridis D, Örey D, et al. 2013. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 382:951–62
Libby AM, Brent DA, Morrato EH, Orton HD, Allen R, Valuck RJ. 2007. Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. *Am. J. Psychiatry* 164:884–91
Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, et al. 2005. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N. Engl. J. Med.* 353:1209–23
Lilienfeld AM 1982. *Ceteris paribus*: the evolution of the clinical trial. *Bull. Hist. Med.* 56:1–18
López-Muñoz F, Alamo CE. 2009. Monoaminergic neurotransmission: the history of the discovery of antidepressants from 1950s until today. *Curr. Pharm. Des.* 15:1563–86
López-Muñoz F, Alamo CE, Shen W, Clervoy P, Rubio G. 2005. History of the discovery and clinical introduction of chlorpromazine. *Ann. Clin. Psychiatry* 17:113–35
Mark TL, Kassed C, Levit K, Vandivort-Warren R. 2012. An analysis of the slowdown in growth of spending for psychiatric drugs, 1986–2008. *Psychiatr. Serv.* 63:13–18
Marks HM. 1997. *The Progress of Experiment*. Cambridge, UK: Cambridge Univ. Press
Maudsley H. 1895. *The Pathology of Mind: A Study of its Distempers, Deformities, and Disorders*. London: Macmillan
Med. Res. Counc. 1948. Streptomycin treatment of pulmonary tuberculosis. *BMJ* 2:769–82
Meltzer HY, Stahl SM. 1976. The dopamine hypothesis of schizophrenia: a review. *Schizophr. Bull.* 2:19–76
Mermelstein MD. 1956. Evaluative study of one hundred transorbital leucotomies. *J. Clin. Psychiatry* 12:271–76
Mojtabai R, Olfson M. 2014. National trends in long-term use of antidepressant medications: results from the US National Health and Nutrition Examination Survey. *J. Clin. Psychiatry* 75:169–77
Olfson M, King M, Schoenbaum M. 2015. Antipsychotic treatment of adults in the United States. *J. Clin. Psychiatry* 76:1346–53
Overholser W. 1956. Has chlorpromazine inaugurated a new era in mental hospitals? *J. Clin. Exp. Psychopathol.* 17:197–201
Pletscher A, Shore PA, Brodie BB. 1955. Serotonin release as a possible mechanism of reserpine action. *Science* 122:374–75
Pow JL, Baumeister AA, Hawkins MF, Cohen AS, Garand JC. 2015. Deinstitutionalization of American public hospitals for the mentally ill before and after the introduction of antipsychotic medications. *Harv. Rev. Psychiatry* 23:176–87
Rasmussen N. 2006. Making the first anti-depressant: amphetamine in American medicine, 1929–1950. *J. Hist. Med. Allied Sci.* 61:288–323
Sadowsky J. 2016. *Electroconvulsive Therapy in America*. New York: Taylor & Francis
Sarwer-Foner GJ. 1960. *The Dynamics of Psychiatric Drug Therapy*. Springfield, IL: Thomas
Schildkraut JJ 1965. The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am. J. Psychiatry* 122:509–22
Schou M, Juel-Nielsen N, Strömgren E, Voldby H. 1954. The treatment of manic psychoses by the administration of lithium salts. *J. Neurol. Neurosurg. Psychiatry* 17:250–60
Scull A 1990. Deinstitutionalization: cycles of despair. *J. Mind Behav.* 11:301–11

Scull A. 2015. *Madness in Civilization: A Cultural History of Insanity, from the Bible to Freud, from the Madhouse to Modern Medicine*. Princeton, NJ: Princeton Univ. Press
Selikoff IJ, Robitzek EH. 1952. Tuberculosis chemotherapy with hydrazine derivatives of isonicotinic acid. *Dis. Chest* 21:385–438
Shorter E. 1997. *A History of Psychiatry: From the Era of the Asylum to the Age of Prozac*. New York: Wiley
Shorter E. 2008. *Before Prozac: The Troubled History of Mood Disorders in Psychiatry*. Oxford, UK: Oxford Univ. Press
Starks SL, Braslow JT. 2005. The making of contemporary American psychiatry, Part 1: Patients, treatments, and therapeutic rationales before and after World War II. *Hist. Psychol.* 8:176–93
Swazey JP. 1974. *Chlorpromazine in Psychiatry: A Study of Therapeutic Innovation*. Cambridge, MA: MIT Press
Tone A. 2008. *The Age of Anxiety: A History of America's Turbulent Affair with Tranquilizers*. New York: Basic Books
Valuck RJ, Libby AM, Orton HD, Morrato EH, Allen R, Baldessarini RJ. 2007. Spillover effects on treatment of adult depression in primary care after FDA advisory on risk of pediatric suicidality with SSRIs. *Am. J. Psychiatry* 164:1198–1205
Veterans Adm. 1956. *Transactions of the First Research Conference on Chemotherapy in Psychiatry: Held April 26 and 27, 1956 at the VA Hospital, Downey, Illinois, by the Psychiatry and Neurology Service, Office of the Assistant Chief Medical Director for Planning, Department of Medicine and Surgery*. Washington, DC: Veterans Adm.
Wang SM, Han C, Lee SJ, Jun TY, Patkar AA, et al. 2018. Efficacy of antidepressants: bias in randomized clinical trials and related issues. *Expert Rev. Clin. Pharmacol.* 11:15–25
Winkelman NW. 1954. Chlorpromazine in the treatment of neuropsychiatric disorders. *JAMA* 155:18–21
Wortis J. 1954. Physiological treatment. *Am. J. Psychiatry* 110:507–11
Zubin J. 1953. Evaluation of therapeutic outcome in mental disorders. *J. Nerv. Ment. Dis.* 117:95–111

Annual Review of
Clinical Psychology

Volume 15, 2019

Contents

Positive Psychology: A Personal History
Martin E.P. Seligman 1

History of Psychopharmacology
Joel T. Braslow and Stephen R. Marder 25

Bifactor and Hierarchical Models: Specification, Inference, and Interpretation
Kristian E. Markon 51

The Utility of Event-Related Potentials in Clinical Psychology
Greg Hajcak, Julia Klawohn, and Alexandria Meyer 71

An Active Inference Approach to Interoceptive Psychopathology
Martin P. Paulus, Justin S. Feinstein, and Sahib S. Khalsa 97

Implicit Cognition and Psychopathology: Looking Back and Looking Forward
Bethany A. Teachman, Elise M. Clerkin, William A. Cunningham, Sarah Dreyer-Oren, and Alexandra Werntz 123

The MMPI-2-Restructured Form (MMPI-2-RF): Assessment of Personality and Psychopathology in the Twenty-First Century
Martin Sellbom 149

Normal Versus Pathological Mood: Implications for Diagnosis
Ayelet Meron Ruscio 179

The Role of Common Factors in Psychotherapy Outcomes
Pim Cuijpers, Mirjam Reijnders, and Marcus J.H. Huibers 207

One-Session Treatment of Specific Phobias in Children: Recent Developments and a Systematic Review
Thompson E. Davis III, Thomas H. Ollendick, and Lars-Göran Öst 233

Augmentation of Extinction and Inhibitory Learning in Anxiety and Trauma-Related Disorders
Lauren A.M. Lebois, Antonia V. Seligowski, Jonathan D. Wolff, Sarah B. Hill, and Kerry J. Ressler 257

Mindfulness Meditation and Psychopathology
Joseph Wielgosz, Simon B. Goldberg, Tammi R.A. Kral, John D. Dunne, and Richard J. Davidson 285

Prenatal Developmental Origins of Future Psychopathology: Mechanisms and Pathways
Catherine Monk, Claudia Lugo-Candelas, and Caroline Trumpff 317

Using a Developmental Ecology Framework to Align Fear Neurobiology Across Species
Bridget Callaghan, Heidi Meyer, Maya Opendak, Michelle Van Tieghem, Chelsea Harmon, Anfei Li, Francis S. Lee, Regina M. Sullivan, and Nim Tottenham 345

Man and the Microbiome: A New Theory of Everything?
Mary I. Butler, John F. Cryan, and Timothy G. Dinan 371

Estrogen, Stress, and Depression: Cognitive and Biological Interactions
Kimberly M. Albert and Paul A. Newhouse 399

Adolescent Suicide as a Failure of Acute Stress-Response Systems
Adam Bryant Miller and Mitchell J. Prinstein 425

Abnormal Sleep Spindles, Memory Consolidation, and Schizophrenia
Dara S. Manoach and Robert Stickgold 451

The Development of the ICD-11 Classification of Personality Disorders: An Amalgam of Science, Pragmatism, and Politics
Peter Tyrer, Roger Mulder, Youl-Ri Kim, and Mike J. Crawford 481

A Reciprocal Model of Pain and Substance Use: Transdiagnostic Considerations, Clinical Implications, and Future Directions
Joseph W. Ditre, Emily L. Zale, and Lisa R. LaRowe 503

Anxiety-Linked Attentional Bias: Is It Reliable?
Colin MacLeod, Ben Grafton, and Lies Notebaert 529

Biomedical Explanations of Psychopathology and Their Implications for Attitudes and Beliefs About Mental Disorders
Matthew S. Lebowitz and Paul S. Appelbaum 555

Psychology's Replication Crisis and Clinical Psychological Science
Jennifer L. Tackett, Cassandra M. Brandes, Kevin M. King, and Kristian E. Markon 579

Errata

An online log of corrections to *Annual Review of Clinical Psychology* articles may be found at http://www.annualreviews.org/errata/clinpsy